Remarks/Arguments

Claims 1-25 and 27-46 are currently pending in the instant application. In view of the finality of the restriction requirement, claims 1-25 are under examination and claims 27-46 have been withdrawn from consideration.

Claims Rejections – 35 USC § 103

Claims 1-25 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Genentech (Basey *et al.*; WO 99/57134) in view of Grandics *et al.* (US 5,571,720).

In view of the arguments presented by Applicants in their Response filed October 17, 2007, the Examiner alleges that "the only issue is whether one of skill in the art would have been motivated to use more than a linear salt gradient (e.g. single pass) in view of Grandics et al." Citing column 7, line 65, thru column 8, line 3, the Examiner asserts that Grandics "teaches a 'non-linear (salt) gradient' option." (Pages 3-4 of the Final Office Action mailed March 17, 2008)

As pointed out in previous Responses of record, an obviousness inquiry is controlled by the factors articulated by the Supreme Court in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), including: 1) the scope and content of the prior art; 2) the differences between the prior art and the claims; 3) the level of ordinary skill in the pertinent art; and 4) objective evidence of non-obviousness. In addition, a long line of Federal Circuit decisions have established that a patent claim is only proved obvious if the prior art, the problem's nature, or the knowledge of a person of ordinary skill in the art provides some motivation or suggestion to combine the prior art teachings (the "teaching, suggestion, or motivation" or "TSM" test). While the Supreme Court has recently rejected a rigid application of the TSM test, it stated that the Graham Deere factors still control an obviousness inquiry. See KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. at 1727. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the Graham analysis." KSR, 127 S. Ct at 1731. The Court specifically acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the

claimed new invention does" in an obviousness determination. *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. *Id.*

Applying these principles, Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness because: (1) the references cited do not teach or suggest all limitations of the currently pending claims, (2) there is no motivation or suggestion to modify the references to reach the Applicants invention, (3) there is no reasonable expectation of success, and (4) the Examiner has based obviousness on improper hindsight.

1. Basey *et al.* does not teach or suggest protein purification via ion exchange chromatography employing different salt gradients resulting in a non-linear salt gradient and Grandic et al. do not cure the deficiencies of Basey *et al.*

Basey *et al.* teaches protein purification by ion exchange chromatography, but does not teach an ion exchange chromatography system where a salt gradient is employed. Grandics *et al.* teach the use of an integrated cell culture protein purification system using an ion exchange chromatography using a single linear salt gradient.

The Examiner asserts that "[c]ontrary to Applicant's conclusion, the Examiner's review of the reference does in fact find that Grandics et al. teaches a "non-linear (salt) gradient" option (see col. 7-8)." (Page 3 of the Final Office Action mailed March 17, 2008)

Applicants respectfully disagree and submit that the Examiner misconstrues the teachings of Grandics *et al.* First, Applicants note that the section of Grandics cited by the Examiner which states, "[u]nbound materials are washed with the binding salt solution and then product is recovered by applying a low salt buffer or a reverse salt gradient onto the cartridge through the gradient former," (column 7, line 67, thru column 8, line 3) does not teach the use of a "non-linear" gradient. Further, this section of the methodology used by Grandics refers specifically to purification using a hydrophobic interaction column (HIC); whereas the instant method is applied to ion exchange chromatography. Nevertheless, contrary to the Examiner's assertion, Grandics provides no further disclosure with respect to the gradient that would indicate a "non-linear" gradient was or could be applied to achieve the desired result. In the absence of specified

parameters used to adjust the gradient, one skilled in the art would assume the " reverse salt gradient" to refer to a linear salt gradient, which means that concentration of salt changes continuously and linearly, either with, for example, time or volume. By contrast, Claim 1 of the present application teaches protein purification via cation exchange chromatography employing different salt gradients resulting in a non-linear salt gradient. Thus the subject matter recited in claim 1 is distinctly different than the combined disclosures of the cited reference, which, at best, could suggest the use of a single, linear salt gradient.

Second, Applicants reiterate that, in the section cited by the Examiner, Grandics teaches the application of a low salt buffer or a reverse salt gradient. While this is common practice in purification methods using hydrophobic interaction columns, it is unsuitable for applications using ion exchange chromotagraphy. In suggesting that one skilled in the art would combine the teachings of Basey, using ion exchange chromotagraphy, and Grandics, using a method reversing the salt concentration from high to low during the washing and elution steps, the Examiner has erred in resolving the level of skill in the art. Clearly, there can be no expectation of success in applying the reverse salt gradient method of Grandics to achieve the instant method which comprises washing the ion exchange resin with a wash buffer, "wherein the salt concentration of the wash buffer increases from an initial, second salt concentration that is greater than the salt concentration of the equilibration buffer, to a final, third salt concentration, and eluting the polypeptide from the ion exchange resin with elution buffer that has a salt concentration that is greater than the final salt concentration of the wash buffer." (Claim 1)

Third, Applicants submit that Grandics *et al.* do not teach applying a salt gradient of any kind, linear or non-linear, during the washing phase of the purification method. It is only when the "product is recovered", or during the elution phase, that Grandics contemplates applying a low salt buffer or a reverse salt gradient. As indicated above, the instant method applies the salt gradients during the washing steps, as well as the elution step, of the purification method.

2. No motivation or suggestion to modify either Basey *et al* or Grandics *et al* to reach the present invention.

The Examiner alleges that the motivation to modify Basey *et al.* (Genentech) to reach the present invention exists because "Grandics et al. advantageously teaches the use of a salt

gradient in a similar ion exchange chromatography system for cell culture protein purification," (Page 4 of the March 17, 2008 Office Action). However, as discussed above, the cited reference fails to provide or suggest a method for purifying a polypeptide that comprises washing the ion exchange resin with a wash buffer, "wherein the salt concentration of the wash buffer increases from an initial, second salt concentration that is greater than the salt concentration of the equilibration buffer, to a final, third salt concentration, and eluting the polypeptide from the ion exchange resin with elution buffer that has a salt concentration that is greater than the final salt concentration of the wash buffer.". In the absence of this subject matter of the claimed invention, there is no motivation in the art to provide the claimed invention.

Even if one of ordinary skill in the art were to be motivated to modify Basey *et al.* in view of some general "advantage" to utilize the linear salt gradient step of Grandics *et al.*, such purification method clearly fails to provide all the elements required of Claims 1-25. Moreover, such a method would not specifically employ different salt gradients resulting in a non-linear salt gradient during the washing phase. Accordingly, even if combined, the cited references fail to provide all the claim elements, and fail to make the present invention obvious.

3. Basey *et al.* in view of Grandics *et al.* fails to provide a reasonable expectation of success for providing protein purification via cation exchange chromatography employing different salt gradients resulting in a non-linear salt gradient.

As stated above, the cited references provide no disclosure of washing the ion exchange resin with a wash buffer, "wherein the salt concentration of the wash buffer increases from an initial, second salt concentration that is greater than the salt concentration of the equilibration buffer, to a final, third salt concentration, and eluting the polypeptide from the ion exchange resin with elution buffer that has a salt concentration that is greater than the final salt concentration of the wash buffer.", and so fails to provide the basis for any expectation of success at all, reasonable or otherwise, for providing protein purification via cation exchange chromatography employing different salt gradients resulting in a non-linear salt gradient. In the absence of any recognition of the claimed subject matter, or of any conception of the claimed subject matter, one of ordinary skill in the art could not have a reasonable expectation of success for providing such (unknown and unrecognized) subject matter.

Accordingly, the cited references fail to provide a reasonable expectation of success for providing the claimed subject matter.

4. The Examiner has based obviousness on improper hindsight.

Applicants respectfully submit that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning. As discussed above, the references cited by the Examiner do not teach or suggest protein purification via cation exchange chromatography employing different salt gradients resulting in a non-linear salt gradient. In addition, given this deficiency, there is no motivation or suggestion to modify Basey *et al.* or Grandics *et* al. to reach the present invention, and no reasonable expectation that a combination of the reference with knowledge in the art would succeed in producing a protein purification method via cation exchange chromatography that employs different salt gradients resulting in a non-linear salt gradient. Indeed, there is no doubt that the Examiner has used the disclosure of the present application to pick and choose selected portions of Basey *et al.* and Grandics *et al.*, anion exchange chromatography and salt gradients, in an attempt to recreate the claimed invention. Applicants respectfully submit that the Examiner's conclusion is based upon an improper hindsight reconstruction of the claimed invention, which, instead of looking at the prior art as a whole, picks and chooses teachings that appears to support a finding of obviousness, while completely disregarding others.

In summary, Applicants have shown that that the Examiner has not established a *prima facie* case of obviousness because: (1) the references cited by the Examiner do not teach or suggest protein purification via cation exchange chromatography employing different salt gradients resulting in a non-linear salt gradient, (2) there is no motivation or suggestion to modify the reference to reach the instant protein purification method because the references do not discloses protein purification via cation exchange chromatography employing different salt gradients resulting in a non-linear salt gradient, (3) there is no reasonable expectation of success that a combination of the references would succeed in producing a protein purification method utilizing cation exchange chromatography and non-linear salt gradients due to the lack of disclosure of washing steps employing different salt gradients resulting in a non-linear salt gradient, and (4) the Examiner has based obviousness on improper hindsight. Accordingly,

Applicants request that the rejection of Claims 1-25 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Basey *et al.* in view of Grandics *et al.* be withdrawn.

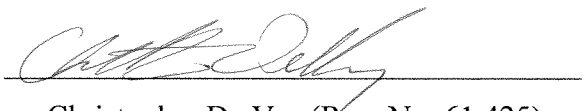
Conclusion

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 50-4634 **(Attorney Docket No.: 123851-181807 (GNE-0113.US))**. Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: December 9, 2008

By 

Christopher De Vry (Reg. No. 61,425)

GOODWIN PROCTER LLP
135 Commonwealth Drive
Menlo Park, California 94025
Telephone: (650) 752-3100
Facsimile: (650) 853-1038

LIBC/3443713.1